A Section 508–conformant HTML version of this article is available at https://doi.org/10.1289/EHP4045.

Impacts of Subchronic, High-Level Noise Exposure on Sleep and Metabolic Parameters: A Juvenile Rodent Model

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Background: Noise is an environmental factor that has been associated with metabolic and sleep disorders. Sleep is a vital function, since it underpins physiologic processes and cognitive recovery and development. However, the effects of chronic noise exposure on the developing organism are still subject to debate.

Objective: The objective of the present study was to assess the effects of subchronic, high-level noise exposure on sleep, apnea, and homeostasis in juvenile rats.

Methods: Twenty-four 3-wk-old male Wistar rats were exposed to noise [87.5 decibels (dB), 50–20,000 Hz] for 5 wk and 2 d during the 12-h rest period. Data on sleep stages, food and water intake, apnea, and body and organ weight were recorded.

Results: Five weeks of high-level noise exposure were associated with hyperphagia (+15%), body weight gain (+6%), a heavier thymus (+26%), and heavier adrenal glands (+117%). A sleep analysis highlighted microstructural differences in the active period: in particular, the mean daily amount of rapid eye movement (REM) sleep as a proportion of total sleep time (TST) was higher. The mean daily amount of non-REM (NREM) sleep was lower in the exposed group, meaning that the intergroup difference in the TST was not significant. During a 1-h, noise-free plethysmographic recording during the rest period, the mean total amount of active wakefulness (AW) was lower in the exposed group (by 9.1 min), whereas the mean duration of an episode of REM sleep was higher (by 1.8 min), and the TST was higher (by 10.7 min).

Discussion: Subchronic exposure of juvenile rats to high-intensity noise during the rest period was associated with some small but significant sleep disturbances, greater food and water intakes, greater body weight gain, and greater thymus and adrenal gland weights. The main effects of noise exposure on sleep were also observed in the 1-h plethysmography session after 5 wk of exposure. https://doi.org/10.1289/EHP4045

Introduction

A third of the world's population suffers from poor-quality sleep and/or a lack of sleep (Ohayon 2011). The main cause of these sleep disturbances is noise exposure (Goines and Hagler 2007). According to the Organisation for Economic Co-operation and Development, in 2001, 13% of European people, corresponding to 100 million, were exposed to noise levels exceeding 65 A-weighted decibels [dB(A)] (OECD 2001). This is despite the fact that 55 dB(A) noise is known to increase the secretion of hormones regulated by the autonomic nervous system and promotes awakening (Fouladi et al. 2012; Zare et al. 2016). Indeed, noise exposure is associated with both auditory and nonauditory effects (including sleep disturbances).

Sleep can be disturbed either directly (when exposure to noise occurs during the sleep period) or indirectly (as an aftereffect, when exposure occurs before the sleep period). Epidemiologic studies of populations living close to airport or major roads have shown that noise exposure during the rest period decreased subjective sleep quality (Frei et al. 2014), increased difficulty in falling asleep (Basner 2008), increased awakenings from sleep, and altered sleep stages [especially a reduction in the proportion of rapid eye movement (REM) sleep] (Hobson 1989; Weyde et al. 2017). Interventional studies in humans have shown that noise during the active period decreased REM sleep duration (Blois et al. 1980), while transient noise up to 71 dB(A) during the rest period did not modify REM duration but increased transient activation phases (Bach et al. 1991). In rats, environmental acute exposure (for 1 d) and pseudochronic exposure (for 9 d) to 85 dB noise during the rest period was found to fragment sleep and reduce the amount of REM sleep, the amount of non-REM (NREM) sleep, and the total sleep time (TST) (Mavanji et al. 2013; Parrish and Teske 2017).

Besides these effects on sleep, epidemiologic studies of adults have linked noise to hyperglycemia (Eze et al. 2017), elevated blood triglyceride levels (Axelsson and Lindgren 1985), elevated waist circumference, and obesity (Pyko et al. 2015). Although it is difficult to established whether these metabolic effects are mediated by sleep disturbances, the latter are known to modify certain metabolic functions, which in turn may result in body weight loss (Moraes et al. 2014) or gain (Michel et al. 2003).

In the literature, most investigators have evaluated the physiologic effects of acute or pseudochronic exposure to noise over periods ranging from 1 h to 9 d, with intensities of 85 to 90 dB (Mavanji et al. 2013; McCarthy et al. 1992; Rabat et al. 2005; Rabat 2007; Van Campen et al. 2002; Zheng and Ariizumi 2007). Only one study (in mice) assessed long-term, subchronic noise exposure (90 dB for 5 h/day over 4 wk), i.e., under conditions that are more representative of the environment commonly encountered by the human population (Zheng and Ariizumi 2007). All the above-cited studies were performed with either environmental noise or artificial (white) noise. Artificial noise is not always appropriate for experiments in the rat because the latter's auditory system is shifted toward higher frequencies than that of humans (Heffner et al. 1994). Environmental noise induced similar sleep disturbances in humans and in rats (Passchier-Vermeer and Passchier 2000; Rabat et al. 2004). Furthermore, in a rodent model, it was shown that environmental noise had a more harmful impact on sleep than continuous white noise did and a similar effect compared with intermittent white noise (Rabat et al. 2004). In the present study, we chose to combine environmental and white noise with a mean intensity of 87.5 dB; this corresponds to high-level exposure but does not perturb the rat's auditory func-

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The authors declare they have no actual or potential competing financial interests.

Received 13 June 2018; Revised 9 April 2019; Accepted 14 April 2019; Published 8 May 2019.

tions, even when administered for long periods (Cappaert et al. 2000).

Most of the literature data on the effects of noise on sleep or metabolic functions were generated in studies of adults; this is despite the fact that sleep processes are particularly relevant for body growth, homeostasis, and brain and organ maturation in developing organisms (Porkka-Heiskanen 2013; Stansfeld and Clark 2015).

The objective of the present study was to analyze the effects of subchronic noise exposure on hypnic and homeostatic parameters in juvenile rats. Sleep, body weight, the weight of several organs, food and water intakes, and episodes of sleep apnea were recorded. The mRNA expression levels of several genes involved in the regulation of food intake (Sohn et al. 2013; Suzuki et al. 2010) [coding for pro-opiomelanocortin (*POMC*), neuropeptide Y (*NPY*), cocaine- and amphetamine-regulated transcript (*CART*), and the leptin receptor] were also assessed. Our starting hypothesis was that juvenile rats exposed to subchronic noise would present sleep and homeostasis disturbances (relative to control, nonexposed animals) and that these disturbances would be associated with developmental changes (e.g., differences in food intake and/or body and organ weights).

Methods

Animals

Experiments were conducted on 24 male Wistar rats (Janvier Labs) weighing between 55 and 85 g and aged 3 wk at the time of their arrival in our facility [day (D)1]. In order to circumvent potentially confounding factors such as menstrual cycles and the impact of hormones on physiological functions (and especially thermoregulatory functions), only male rats were studied here. Two groups of animals were formed: a noise-exposed group ($n = 12$) and a control, nonexposed group ($n = 12$). Two series of animals were studied: 2×6 exposed rats and 2×6 control rats. The rats were randomly assigned 1:1 to the two study groups. The difference in body weight between the noise-exposed group and the nonexposed group was not statistically significant [mean ± standard deviation (SD): 68.68 ± 6.89 g vs. 67.87 ± 10.16 g, respectively]. Each group was housed in a separate anechoic chamber with a controlled thermoneutral air temperature ($24 \pm 1°C$), 12 h: 12 h dark/light cycle (lights on at 0600 hours and off at 1800 hours), relative air humidity (mean ± SD: $39 \pm 12\%$), and air velocity (<0.2 m/s). Rats were individually housed in plastic cages (425 mm × 266 mm × 185 mm) within the chamber. Food (3436 EXF12; Serlab) and water were available *ad libitum*. Daily animal care was performed between 1700 and 1800 hours. Experiments were performed in accordance with the European guidelines (2010/63/EU) and the French governmental decree 2013-118 on the care and use of laboratory animals. The study protocol was approved by the nationally accredited Regional Directorate for Health, Animal and Environment Protection (Amiens, France) and the French Ministry of Research (license number: APAFIS#3,735-2016012017118094 v3).

Noise Exposure

The noise exposure protocol was initiated after 4 d of adaptation and continued for the following 5 wk and 2 d (i.e., from D5 to D41). Rats were exposed for 36 d, which corresponds to the duration of body growth in the rat. At D41, a rat is considered to be a young adult with regard to the physiological functions studied here (Spear 2000). Exposed animals were subjected to a 24-h soundtrack divided into two main periods: a noise-free active period from 1700 to 0600 hours, and a noisy rest period (the rat's sleep period) from 0600 to 1700 hours. The high-level noise exposure was therefore temporarily interrupted during handling and during plethysmographic measurements (between 1700 and 1800 hours, when the intensity of the background noise was 65 dB).

The noise exposure period was split into 10-min segments, each of which had a unique combination of noise type, frequency, and intensity. The noise types were urban sounds (traffic, roadworks, sirens, etc.), music, and artificial sounds (white noise, red noise, sinusoids, etc.). The mean ± SD (range) sound level was 87.5 ± 3.7 dB (59–111 dB). The frequencies ranged from 50 to 20,000 Hz. To avoid habituation, four different 24-h noise exposure files were built out of 10-min segments arranged in a pseudorandom order. Each day's noise exposure file was chosen in a pseudorandom manner. The noise was regulated by an amplifier (COMBO-130; Audiophony Hit Music SAS) and delivered through loudspeakers (K50, 8 ohms, JBSystems).

Study Design

After 4 d of habituation to housing conditions (Figure 1), animals were exposed (or not) to noise for 5 wk and 2 d (until D41). On D26 or D27, a telemetric sensor was surgically implanted in each animal. From D33 to D39, electroencephalography (EEG), electromyography (EMG), food intake, water intake, and body weight data were recorded. At D41, the rats were sacrificed by heart puncture under general anesthesia with a mixture of air and 2.5% isoflurane (Iso-Vet 1,000 mg/g; Piramal Enterprises Limited), and the brain, heart, bronchial tree, spleen, thymus, liver, kidney, and salivary and adrenal glands were collected and weighed. Then the hypothalamuses were separated from the brain and put into a tube containing RNA*later*™ stabilization solution (Ambion) and frozen immediately at −80°C until RNA extraction procedure. The other organs were also stored at −80°C.

Telemetric Implant Surgery

A subcutaneous telemetric EEG and EMG sensor (F20-EET; Data Sciences International) was implanted under general anes-

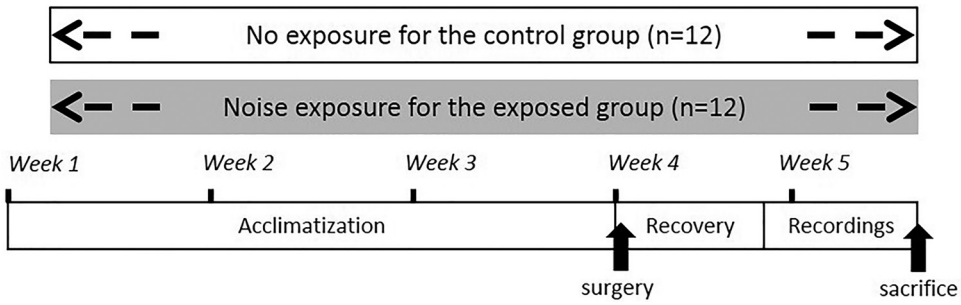

Figure 1. Study design. Because of analysis protocol problem, mRNA expression genes were only analyzed for 11 of the 12 control animals. Because of technical problems, sleep parameters were only calculated for 10 of the 12 noise-exposed animals.

thesia with isoflurane (5% for induction, and then 2.5% during surgery). After the first sign of anesthesia, the animals were placed on a heating pad (Thermoplasme). The fur on the head and the neck were clipped from the margin of the eyes to scapulae in a strip 2 cm wide. The surgical site and surrounding area were swabbed with Vétédine® (Vétoquinol). A 4- to 5-cm incision was made through the skin along the dorsal midline from the posterior margin of the eyes to a point midway between the scapulae. The skull of tissue was cleared down to the bone using a cotton-tipped applicator soaked in 3% hydrogen peroxide. To record the frontoparietal EEG signal, two holes were bored through the skull at the right of the animal with a drill, with care taken to not perforate the dura matter. The surface of the skull was etched using a scalpel blade to increase the adhesion between the bone and dental cement. Then, two gold-plated screws (15 SURTEX®; Dentatus AB) were inserted just above the dura matter. The electrodes were wound around the screws, and dental cement (Dentalon; Henri Schein) was used to fix the probe and isolate the EEG signal. To measure the EMG signal in order to discriminate wakefulness and REM sleep, two electrodes of the implant were inserted directly into the dorsal muscles of the neck (one per side) and sutured to the muscles through a nonabsorbable suture silk. Using blunt-tipped scissors, a subcutaneous pocket was formed along the dorsal neck between the forelimb and the hind limb, and the device was placed into this pocket. The incision was closed with a nonabsorbable suture silk. Before awakening, animals received an intraperitoneal dose (0.05 mg/kg) of buprenorphine (Axience). After surgery, animals were allowed to recover for 5 or 6 d, depending on whether surgery had been performed on D26 or D27.

Data Acquisition and Analysis

Body and organ weights. The animals' body weight was measured every other day using scales (Scaltec SPO-62; Scaltec Instruments; sensitivity: 0.1 g). The weight gain was calculated as follows: weight gain = weight at Day_x − weight at Day_1 in which Day_x indicated the day at x time of experiment and Day_1 indicated the first day of experiment (arrival day of animals).

After sacrifice, the organs were weighed using high-precision scales (Sartorius BP211D; Sartorius Lab Instruments GmbH; sensitivity: 0.01 mg). The weight was expressed as a percentage of the body weight.

Food and water intakes. Daily food intake was recorded with individual scales (Sartorius TE601; Sartorius Lab Instruments GmbH; sensitivity: 0.1 g) placed under the manger and connected to a computer, which detected the time, the duration (in seconds), and the quantity of each meal (in grams) using homemade software. Using this information, we calculated the number of meals per 24 h, the total quantity of food intake per day (in grams per day), the mean quantity of food consumed per meal (in grams per meal), and the mean meal duration per meal (in seconds per meal). We also calculated the total quantity of food intake/body weight ratio, since the food intake is proportional to body weight.

Water intake was measured daily, using individual nursing bottles (sensitivity: 5 mL).

Sleep. The EEG and EMG sensors were connected wirelessly to a receiver (RPC-1; Data Sciences International) and a computer via a matrix (Data Exchange Matrix; Data Sciences International). Data were recorded using Ponemah software (version 6.32; Data Sciences International).

Recordings were scored visually every 4 s with Spike2 software (version 7.01; Cambridge Electronic Design) as AW, quiet wakefulness (QW), NREM sleep, and REM sleep. QW was defined as a short episode (lasting between 8 s and 2 min) of wakefulness within a sleep episode, and during which the animal did not move or eat (Pelletier et al. 2013). AW was defined as a long episode (>2 min) of wakefulness during which the animal was active (eating, grooming, exploring, etc.). For NREM and REM sleep, the total amount (in min per 24 h), episode frequency (per hour), mean episode duration (in minutes), and proportion of TST (in percentage) were calculated.

Due to technical problems, sleep parameters could not be calculated for 2 of the 12 noise-exposed animals.

Apnea. On D40, the number and duration of apnea episodes over a 1-h period were measured using whole-body plethysmography (Model PLY3213; Buxco-EMKA Technologies) during the rest period but in the absence of high-level noise exposure. Rats were familiarized with the plethysmograph for 30 min the day before the measurement and then for 45 min on the day of the measurement. Noise-exposed animals were kept away from noise exposure for 105 min before the measurement. Sleep parameters and apnea events (defined as the cessation of ventilation for at least 2.5 s, i.e., at least two missed breaths) were recorded.

Reverse transcription polymerase chain reaction. Because of analysis protocol problem, mRNA gene expression were only analyzed for 11 of the 12 control animals. Total RNA was isolated from hypothalamic samples using the GenUp™ Total RNA kit (biotechrabbit) according to the manufacturer's instructions. After determination of the RNA concentration using a nanovolume system (Nanodrop 1000 Spectrophotometer; Thermo Scientific), 2 μg of RNA were used for cDNA synthesis with the High Capacity cDNA Reverse Transcription Kit (Applied Biosystems). For transcript detection with quantitative real-time polymerase chain reactions (qPCRs), primers (Table 1) were purchased from Life Technologies, and SYBR™ Green Master Mix (Applied Biosystems™) was used. PCRs were run on an ABI Prism 7900HT Real-Time PCR System (Applied Biosystems™). The housekeeping genes coding for glyceraldehyde 3-phosphate dehydrogenase (*Gapdh*) and β-actin were used as endogenous controls.

The PCR conditions were as follows: denaturation for 1 min at 95°C, annealing at between 58 and 60°C (depending on the primer), and elongation for 2 min at 72°C. All PCR reactions were performed in duplicate. The results were expressed in arbitrary units using a 2-δδCt calculation, relative to the control samples ($\delta\delta Ct = \delta Ct_{exposed} - \text{mean } \delta Ct_{control}$). The expression level of each gene studied was the same relative to *Gadph* and relative to β-actin mRNA, and so all results were expressed relative to *Gadph* only in the final analysis.

Statistical analysis. Data (expressed as the mean ± SD) were analyzed using Statview software (version 5.0; SAS Institute Inc.). When the data were normally distributed (according to a Kolmogorov-Smirnov test), a two-way analysis of variance (with Fisher's partial least-squares difference posttest) was applied to probe the effects of noise exposure and the active/rest period on sleep and food intake parameters. If the data were not normally distributed, a Mann-Whitney test was applied. The threshold for statistical significance was set to $p < 0.05$.

Results

Body and Organs Weights. On D41, the mean ± SD body weight was higher in the noise-exposed group (290.6 ± 33.3 g) than in the control (nonexposed) group (279.5 ± 26.7 g), although this difference did not achieve statistical significance (Table 2). However, the mean ± SD body weight gain between D1 and D41 was significantly higher in the noise-exposed group (222.7 ± 28.8 g) than in the control group (210.8 ± 25.5 g; $p = 0.043$).

Table 1. Primer sequences used for reverse transcription polymerase chain reactions (RT-PCRs).

Gene	Primer sequence: forward (5′–3′)	Primer sequence: reverse (5′–3′)
Rat *Gadph*	F:5′-AGACAGCCGCATCTTCTTGT-3′	R:5′-CTTGCCGTGGGTAGAGTCAT-3′
β-actin	F:5′-AGATCAAGATCATTGCTCCTCCT-3′	R:5′-ACGCAGCTCAGTAACAGTCC-3′
POMC	F:5′-GACCAAACGGGAGGCGACGG-3′	R:5′-GGCTCTGTCGCGGAAAGGCA-3′
CART	F:5′-GGACATCTACTCTGCCGTGG-3′	R:5′-GCGTCACACATGGGGACTT-3′
NPY	F:5′-CCGCCCGCCATGATGCTAGG-3′	R:5′-GGCCATGTCCTCTGCTGGCG-3′
Leptin receptor	F:5′-CCAGTACCCAGAGCCAAAGT-3′	R:5′-GGGCTTCACAACAAGCATGG-3′

Note: *CART*, cocaine- and amphetamine-regulated transcript; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; *NPY*, neuropeptide Y; *POMC*, pro-opiomelanocortin.

The mean ± SD absolute weights of the thymus and adrenal glands and their weights relative to body weight were significantly higher in the noise-exposed group. There were no significant differences between the noise-exposed group and the control group in weight for the brain, heart, lungs, spleen, liver, bronchial tree, salivary glands, and kidneys.

Food and Water Intakes. As shown in Table 3, exposed animals ate more than control animals during both the rest and active periods; the mean total daily food intake was 2.7 g higher ($p < 0.0001$), the number of meals per 24 h was 1.2 higher ($p = 0.001$), and the meal duration was 2.6 min longer ($p = 0.002$) when considering pooled data from the rest and active periods. The mean water intake was 7.3 mL higher in the exposed group ($p = 0.008$). The total quantity of food intake/body weight ratio was higher in the noise-exposed group than in the nonexposed group (0.073 ± 0.008 vs. 0.066 ± 0.006, respectively; $p < 0.0001$).

Sleep. **Sleep analysis per 24-h period.** In the control group, the total amounts of AW and REM sleep were lower during the rest period than during the active period, and the total amount of QW, the total amount of NREM sleep, and the TST were higher (Table 4). Moreover, AW episodes were less frequent during the rest period, whereas QW and NREM sleep episodes were more frequent. On average, the QW episodes were longer during the rest period, whereas the AW and REM episodes were shorter.

Noise exposure was associated with significant differences in the sleep structure (relative to the control group) during both the 24-h rest and active periods (Table 4). There was a noise effect on sleep, since QW and NREM sleep were less frequent in the exposed group than in the control group (by 2.2 and 2.5 episodes/h, respectively), and the mean duration of NREM sleep episodes was greater (by 0.26 min) when considered in the 24-h period. The other effects depended on the nycthemeral period; there was a significant interaction between the period (active, rest) and noise exposure. An intergroup difference was observed during the active period only. Thus, the total amount and the frequency of NREM sleep had a nonsignificant trend to be 22.6 min and 2.5 episodes/h lower in the exposed group ($p = 0.062$ and $p = 0.061$, respectively) during the active period only. Furthermore, the NREM/TST ratio was lower in the exposed group (by 3.1%), whereas the REM/TST ratio was higher (by 3.1%) during the active period only.

Sleep during the plethysmographic recordings, in the absence of high-level noise exposure. Noise exposure was also associated with differences in the sleep structure during a 1-h, noise-free plethysmographic recording during the rest period (Table 5). Relative to the control group, the noise-exposed group displayed a significantly lower total amount of AW (by 9.1 min). There was a nonsignificant trend towards a lower AW frequency (by 1.02 episode/h; $p = 0.069$) in the exposed group. The TST was higher in the exposed group (by 10.7 min) as a result of significant increase in the total duration of REM sleep and nonsignificant trend of increase of NREM (by 1.8 min and 8.9 min, respectively; $p = 0.037$ and $p = 0.057$). There was an intergroup difference in the NREM/TST and REM/TST sleep ratio with a nonsignificant trend. The ratio REM/TST was 3.9 points higher in the exposed group ($p = 0.068$), and NREM/TST was 3.9 points lower ($p = 0.068$). REM sleep episodes were more frequent (by 2.6 episodes) in the exposed group, and the mean duration of NREM sleep episodes was longer (by 1.0 min). There was no significant intergroup difference with regard to QW.

Apnea. Noise exposure was not associated with a significant intergroup difference in the frequency of apnea (7.3 ± 7.8 episodes/h in the control group vs. 9.6 ± 8.4 episodes/h in the exposed group; not significant) or the mean duration of an episode of apnea (3.2 ± 0.5 vs. 3.1 ± 0.3 s, respectively; not significant) during the whole sleeping period.

Gene expression in the hypothalamus. There was no intergroup difference in the mRNA gene expression level for either *POMC* or *NPY*. Relative to the control group, *CART* mRNA expression levels were significantly higher in the exposed group,

Table 2. Initial and final body weight and absolute and relative organ weight in the control group ($n = 12$) and in the exposed group ($n = 12$) at day 41.

	Control group		Noise-exposed group			
Measurement	Weight (g)	Relative weight (%)[a]	Weight (g)	*p*-Value	Relative weight (%)[a]	*p*-Value
Initial body weight	68.68 ± 6.89	N/A	67.87 ± 10.16	NS	N/A	N/A
Final body weight	279.5 ± 26.7	N/A	290.6 ± 33.3	NS	N/A	N/A
Body weight gain	210.8 ± 25.5	N/A	222.7 ± 28.8	0.043	N/A	N/A
Thymus	0.78 ± 0.11	0.26 ± 0.05	0.98 ± 0.22	0.024	0.30 ± 0.05	0.029
Adrenal glands	0.06 ± 0.02	0.02 ± 0.01	0.13 ± 0.10	0.018	0.04 ± 0.03	0.049
Brain	1.69 ± 0.09	0.56 ± 0.05	1.76 ± 0.15	NS	0.55 ± 0.08	NS
Spleen	0.97 ± 0.23	0.32 ± 0.06	1.01 ± 0.22	NS	0.31 ± 0.05	NS
Liver	10.62 ± 1.27	3.48 ± 0.25	12.01 ± 1.78	NS	3.68 ± 0.34	NS
Kidney	2.13 ± 0.24	0.70 ± 0.05	2.21 ± 0.26	NS	0.68 ± 0.08	NS
Bronchial tree	1.41 ± 0.18	0.46 ± 0.04	1.61 ± 0.20	NS	0.49 ± 0.06	NS
Salivary glands	0.54 ± 0.05	0.18 ± 0.01	0.64 ± 0.14	NS	0.19 ± 0.03	NS
Heart	1.9 ± 0.14	0.039 ± 0.05	1.22 ± 0.25	NS	0.37 ± 0.06	NS

Note: Data are expressed as the mean ± standard deviation. The noise-exposed group was exposed to noise at an intensity of 87.5 decibels (dB) and frequencies between 50–20,000 Hz for 5 wk and 2 d during the 12-h rest period. Statistical significance was determined using Mann-Whitney test. N/A, nonapplicable measurement; NS, nonsignificant. *p*-Values are compared to control group.

[a]Ratio between organ weight and animal weight.

Table 3. Food and water intakes in the control group ($n = 12$) and the noise-exposed group ($n = 12$) per 24 h, during the rest period and the active period.

Parameter	Control group			Noise-exposed group			Group comparison		
Period	24 h	Rest period[a]	Active period[b]	24 h	Rest period[a]	Active period[b]	24 h	Rest period[a]	Active period[b]
Food intake: number of meals	12.2 ± 2.2	2.4 ± 1.7	9.4 ± 1.7	13.4 ± 2.6	3.0 ± 1.5	10.2 ± 2.4	$p = 0.001$	$p = 0.025$	$p = 0.035$
Food intake: Total quantity per day (g/d)	18.5 ± 2.4	2.5 ± 1.5	16.5 ± 2.3	21.2 ± 3.0	3.2 ± 1.3	18.1 ± 2.6	$p < 0.0001$	$p = 0.0005$	$p < 0.0001$
Food intake: Mean meal quantity (g/meal)	1.6 ± 0.3	0.9 ± 0.4	1.8 ± 0.4	1.7 ± 0.4	1.0 ± 0.4	1.9 ± 0.5	NS	$p = 0.05$	$p = 0.069$
Food intake: Mean episode duration (min)	11.1 ± 3.8	5.0 ± 3.8	13.0 ± 4.7	13.7 ± 5.4	7.1 ± 4.8	16.2 ± 6.9	$p = 0.002$	$p = 0.005$	$p = 0.002$
Water intake: total quantity (mL)	28.9 ± 6.7	N/A	N/A	36.2 ± 24.7	N/A	N/A	$p = 0.008$	N/A	N/A

Note: Data are expressed as the mean ± standard deviation; Noise-exposed group was exposed to noise at an intensity of 87.5 decibels (dB) and frequencies between 50–20,000 Hz for 5 wk and 2 d during the 12 h rest period. Statistical significance was determined using Mann-Whitney test. N/A, not applicable; NS, nonsignificant. *p*-Values represent significant differences compared to control group.
[a]Resting period with noise exposure.
[b]Active period without noise exposure.

whereas leptin receptor mRNA expression was significantly lower (Table 6).

Discussion

To the best of our knowledge, the present study is the first to have evaluated the effects of subchronic rest time exposure to high-level noise on the main physiological functions involved in the control of body energy balance (sleep, respiration, and energy intake) in growing organisms. This study focused on the impact on adults rats of exposure to subchronic noise during development. The rat is a good model for studying the effects of noise exposure at the intensities and the frequencies chosen, since the slope of the relationship between the animal's compound threshold shift and the noise level is similar to that observed in humans (Chen et al. 2014). Moreover, the critical noise level above which noise-induced hearing loss occurs is similar in rats and humans (Chen et al. 2014). Thus, we could evaluate the effects of environmental noise commonly encountered in humans while being able to control the exposure (in terms of intensity, frequency, etc.). Our results indicated that subchronic, high-level noise exposure during the rest time period was associated with sleep disturbances, elevated body and organ weights, and greater food and water intakes in juvenile rats.

In contrast, we did not observe an intergroup difference in the frequency or duration of apnea episodes. To the best of our knowledge, the incidence of noise exposure on physiological apnea has not previously been studied. Our finding was nevertheless surprising because a multitude of risk factors (age, sex, obesity, craniofacial anatomy, etc.) are associated with apnea in humans (Punjabi 2008). This association is particularly strong for body weight (Punjabi 2008). Unfortunately, we were unable to analyze apnea as a function of the sleep state because *a*) only 16% of the animals experienced an apnea episode during REM sleep, and *b*) the intragroup variability in the frequency of apnea episodes was high.

When considering the 24-h period as a whole, the effects of noise exposure on sleep were small: a lower frequency and a longer mean episode duration for NREM sleep. Interestingly, the effects of noise exposure appeared to depend on the nycthemeral period. During the rest period with noise exposure, the only notable changes were related to NREM sleep [i.e., direct effects of noise that were consistent with previous observations of humans exposed to noise during the rest period (Cantrell 1974; Muzet et al. 1974)]. Sleep was altered more markedly during the active (noise-free) period, i.e., as aftereffects: a lower total amount of NREM sleep, an increase in the total amount of REM sleep, and thus a lower NREM/REM sleep ratio. During a 1-h, noise-free daytime plethysmography session, the sleep parameters were modified even more markedly: the TST was 10.7 min longer in the exposed group as a result of increases in the total amounts of NREM sleep and (especially) REM sleep. The NREM/REM sleep ratio was therefore lower in the exposed group than in the control group.

The very small effects of noise on sleep in our study (with regard to the 24-h period in general and the rest time exposed period in particular) raise the question of whether the noise level was too low to elicit physiological effects. In the literature, rodent sleep was perturbed by (for example) 12 h of acute exposure to 85 dB noise during the sleep period (Parrish and Teske 2017) and by subchronic exposure to 85 dB noise (8 h per day during the rest period, for a total of 9 d) (Mavanji et al. 2013). In humans, 8 nights of exposure to 76 dB(A) noise were associated with marked sleep perturbations (Ehrenstein and Muller-Limroth 1980). Hence, these literature data suggest that the noise intensity applied in the present study was not inadequate.

Differences in the models and in the experimental protocols make it difficult to compare the effects observed here with those in the literature. As mentioned by Dijk et al. (2000), differences might be particularly due to the animals' age (with younger animals used in our study) because sleep is known to be age dependent. Vallet et al. reported that chronic noise exposure was associated with a relative reduction in NREM sleep in people (<45 y old) and a relative reduction in REM sleep in older people (>45 y old) (Vallet et al. 1983). However, the observation of relevant effects without noise during the active period (e.g., food and water intake and various sleep parameters) and during the rest period (e.g., plethysmography parameters) might suggest an impact of sleep habituation and/or sleep pressure.

Firstly, with regard to habituation, studies of noise exposure in young adults have highlighted differences between acute and subchronic conditions, with a lower amount of NREM sleep after 1 d of exposure and then a lower amount of REM sleep after 2 d of exposure (Ehrenstein and Muller-Limroth 1980). To the best of our knowledge, habituation effects have not previously been studied in animals. In the present study, the fact that 5 wk of subchronic exposure were associated with small effects on sleep may have resulted from habituation, i.e., with a fall in the magnitude of the effects of noise over time. However, the greater effects on sleep observed in the noise-free active period (e.g., food and water intake and various sleep parameters) and the noise-free rest period (e.g., plethysmography parameters) are not consistent with this hypothesis.

Secondly, one can hypothesize that sleep pressure masks the harmful effects of noise during the exposed period. Sleep pressure is one of the processes underlying sleep regulation, which implicates mechanisms augmenting sleep propensity when prior

Table 4. Sleep parameters in the control group ($n = 12$) and the exposed group ($n = 10$) during the rest period and the active period.

	Control group			Noise-exposed group			Effects		
Parameters	24 h	Rest period[a]	Active period[b]	24 h[c]	Rest period[a]	Active period[b,d]	Effect of period[e]	Effect of group[f]	Period x group interaction[g]
AW: total duration (min)	557.4 ± 33.6	152.3 ± 25.4	394.9 ± 32.5	569.0 ± 60.1	138.8 ± 28.3	419.1 ± 47.0	$p < 0.0001$	NS	NS
AW: frequency (episodes/h)	1.39 ± 0.36	1.28 ± 0.46	1.47 ± 0.41	1.32 ± 0.45	1.03 ± 0.35	1.59 ± 0.90	$p = 0.035$	NS	NS
AW: mean episode duration (min)	17.9 ± 5.4	10.9 ± 3.7	23.9 ± 7.1	19.5 ± 6.1	12.2 ± 3.6	27.5 ± 13.2	$p < 0.0001$	NS	NS
QW: total duration (min)	136.2 ± 36.0	98.4 ± 29.3	40.3 ± 10.3	126.4 ± 25.3	95.4 ± 20.1	33.5 ± 11.7	$p < 0.0001$	NS	NS
QW: frequency (episodes/h)	15.1 ± 2.0	21.0 ± 3.3	9.7 ± 1.6	12.9 ± 2.0*	18.9 ± 2.6	7.3 ± 2.1	$p < 0.0001$	$p = 0.005$	NS
QW: mean episode duration (min)	0.374 ± 0.074	0.387 ± 0.079	0.346 ± 0.071	0.407 ± 0.064	0.419 ± 0.074	0.375 ± 0.061	$p = 0.059$	NS	NS
TST: total duration (min)	746.3 ± 45.7	469.3 ± 36.0	284.8 ± 29.9	744.6 ± 47.5	485.8 ± 36.2	267.4 ± 36.4	$p < 0.0001$	NS	NS
NREM sleep: total duration (min)	634.5 ± 42.1	417.4 ± 29.3	225.3 ± 26.0	631.9 ± 35.9	438.5 ± 33.5	202.7 ± 27.5#	$p < 0.0001$	NS	$p = 0.017$
NREM sleep: frequency (episodes/h)	16.5 ± 1.9	22.3 ± 3.2	11.2 ± 1.7	14.0 ± 2.0**	19.9 ± 2.8	8.7 ± 2.2#	$p < 0.0001$	$p = 0.003$	NS
NREM sleep: mean episode duration (min)	1.622 ± 0.220	1.596 ± 0.275	1.695 ± 0.238	1.882 ± 0.216*	1.857 ± 0.283	2.010 ± 0.482	NS	$p = 0.006$	NS
NREM sleep: NREM (% of TST)	85.0 ± 1.1	89.0 ± 2.7	79.0 ± 2.3	84.9 ± 2.7	90.3 ± 2.9	75.9 ± 3.7*	$p < 0.0001$	NS	$p = 0.017$
REM sleep: total duration (min)	111.7 ± 8.8	51.9 ± 14.6	59.5 ± 8.3	112.6 ± 23.4	47.3 ± 15.1	64.7 ± 14.1	$p = 0.003$	NS	NS
REM sleep: frequency (episodes/h)	4.21 ± 0.96	4.58 ± 1.32	3.87 ± 0.73	3.97 ± 1.1	4.18 ± 1.53	3.78 ± 0.83	NS	NS	NS
REM sleep: mean episode duration (min)	1.14 ± 0.21	0.96 ± 0.19	1.33 ± 0.33	1.20 ± 0.14	0.96 ± 0.26	1.42 ± 0.25	$p < 0.0001$	NS	NS
REM sleep: REM (% of TST)	15.0 ± 1.1	11.0 ± 2.7	21.0 ± 2.3	15.0 ± 2.7	9.7 ± 2.9	24.1 ± 3.7*	$p < 0.0001$	NS	$p = 0.017$

Note: Data are expressed as the mean ± standard deviation. The noise-exposed group was exposed to noise at an intensity of 87.5 decibels (dB) and frequencies between 50–20,000 Hz for 5 wk and 2 d during the 12-h rest period. Statistical significance was determined using analysis of variance. AW, active wakefulness; NREM, nonrapid eye movement; QW, quiet wakefulness; REM, rapid eye movement; TST, total sleep time.

[a]Rest period with noise exposure.

[b]Active period without noise exposure.

[c]Asterisks represent significant differences compared to control group (*$p < 0.05$; **$p < 0.01$).

[d]The signs represent significant differences compared to control group for the active period only (*$p < 0.05$; #$0.1 < p < 0.05$).

[e]p-Values represent significant differences between the rest period and the active period, whatever the considered group (NS, nonsignificant).

[f]p-Values represent significant differences between the control group and the noise-exposed group, whatever the considered period (NS, nonsignificant).

[g]p-Values represent significant interaction between the two factors: noise exposure and nycthemeral period (NS, nonsignificant).

sleep is curtailed or absent (Borbély 1982). Hence, we looked at whether aftereffects of noise, and a sleep rebound could be seen among the data collected during the noise-free active period. Even though the TST during the experiment as a whole did not differ significantly in the exposed and control groups, exposed animals slept more when the noise exposure was briefly interrupted during the 1-h plethysmographic recording. In the exposed group, the TST was 10.7 min greater, and the NREM/REM sleep ratio was lower. One can therefore hypothesize that even though the sleep quality was inadequate in animals exposed to noise (as evidenced by slight modifications in sleep structure), sleep pressure can overcome harmful effects of noise during the rest period (i.e., with a slight sleep rebound during the following night).

The hypnic effects observed here might be due to noise-induced stress. The lack of significant active time aftereffects on TST is in contradiction with the results of studies performed in adult humans (Blois et al. 1980; Fruhstorfer et al. 1988). This apparent discrepancy between the lack of significant active time aftereffects on TST and the greater TST during the rest time plethysmography session in the exposed group might be due to the difference in the time interval between sleep onset and the end of the noise exposure (30 min for the plethysmography session but 60 min for the 24-h recording). Averaging TST over the 12-h active period might mask effects occurring in the first few hours of the following active period (Bach et al. 1991). Regardless of whether sleep pressure and/or stress had effects, it is important to bear in mind the fact that noise exposure was not associated with a difference in the TST or the rest period vs. active period sleep distribution.

In the present study, the animals in the exposed group gained more body weight (by 6%, on average) than control animals did. This gain was accompanied by greater food and water intakes. It is possible that a longer period of noise exposure might have caused the elevate body weight to reach a pathological threshold. In previous studies of adult rats exposure to subchronic noise (85 dB for 12 h a day over 9 d), weight gain was associated with greater food intake in one study (Mavanji et al. 2013) but not in others (Parrish and Teske 2017). Another study of chronic (30-d), single-tone (2,640 Hz) noise exposure (dB not indicated) reported low food intake and body weight in the rats (Alario et al. 1987). Our data on metabolic parameters might reflect both a direct effect of noise exposure and also an indirect effect through sleep perturbation. Indeed, body weight gain was also observed when sleep duration was restricted in animals (Wang et al. 2014), healthy adult humans (Calvin et al. 2013; Spaeth et al. 2013), children in the general population (Spiegel et al. 2004; von Kries et al. 2002), and children with metabolic disorders (Vgontzas et al. 2008).

The mRNA expression level of *CART* was significantly greater in the exposed group, while the expression level of the leptin receptor was lower. There were no significance intergroup differences in expression for *NPY* and *POMC*. The reduction in leptin receptor mRNA levels might explain (at least in part) the hyperphagia observed in noise-exposed animals, even though the mRNA expression level of *NPY* did not differ significantly.

Thus, the greater body weight gain, food and water intakes, and the differences in leptin receptor and *CART* gene expression observed in the present study might indicate a risk of metabolic disease (such as diabetes or obesity), as has already been observed in epidemiologic studies of people exposed to noise (Sørensen et al. 2013). To confirm this hypothesis, it could be interesting to compare our results with results from a reverse protocol for which the noise exposure will be during the active period and the rest period will be without noise.

Table 5. Sleep parameters in the control group ($n = 12$) and the noise-exposed group ($n = 10$) measured during a 1 h of rest period, noise-free plethysmography session on D40.

Parameters	Control group	Noise-exposed group	Group comparison
AW: total duration (min)	18.9 ± 16.3	9.8 ± 8.5	$p = 0.035$
AW: frequency (episodes/h)	2.39 ± 1.62	1.37 ± 0.75	$p = 0.069$
AW: mean episode duration (min)	9.6 ± 12.6	5.7 ± 6.1	NS
QW: total duration (min/h)	5.3 ± 3.3	7.0 ± 3.3	NS
QW: frequency (episodes/h)	13.05 ± 6.92	14.93 ± 6.83	NS
QW: mean episode duration of the (min)	0.4 ± 0.2	0.5 ± 0.2	NS
TST: total duration (min)	32.5 ± 13.9	43.2 ± 7.1	$p = 0.032$
NREM sleep: total duration (min)	31.5 ± 13.1	40.4 ± 7.0	$p = 0.057$
NREM sleep: frequency (episodes/h)	15.44 ± 7.39	15.95 ± 6.90	NS
NREM sleep: mean episode duration (min)	2.0 ± 0.9	3.0 ± 1.3	$p = 0.059$
NREM sleep: percentage of TST	97.42 ± 3.48	93.57 ± 5.63	$p = 0.068$
REM sleep: total duration (min)	1.0 ± 1.5	2.8 ± 2.3	$p = 0.037$
REM sleep: frequency (episodes/h)	1.19 ± 1.74	3.76 ± 2.63	$p = 0.011$
REM sleep: mean episode duration (min)	0.7 ± 0.6	0.7 ± 0.4	NS
REM sleep: percentage of TST	2.58 ± 3.48	6.43 ± 5.63	$p = 0.068$

Note: Data are expressed as the mean ± standard deviation. Noise-exposed group was exposed to noise at an intensity of 87.5 decibels (dB) and frequencies between 50–20,000 Hz for 5 wk and 2 d during the 12-h rest period. Statistical significance was determined using analysis of variance. AW, active wakefulness; NREM, nonrapid eye movement; NS, nonsignificant; QW, quiet wakefulness; REM, rapid eye movement; TST, total sleep time. *p*-Values represent significant differences compared with control group.

The only intergroup differences in absolute and relative organ weights were observed for the adrenal glands and the thymus, with higher weights in the exposed group. It would have been interesting to measure blood corticosterone levels, since organ hypertrophy can result from the high levels of adrenocorticotropic hormone induced by primary hypothalamic disease or glucocorticoid feedback dysregulation (Harvey and Sutcliffe 2010). Indeed, Gamallo et al. demonstrated that noise exposure increased the secretion of corticosterone in the absence of adrenal gland hypertrophy (Gamallo et al. 1988). Functional adrenal gland disorders in rats have previously been linked to changes in body weight gain (Alario et al. 1987).

The greater mean thymus weight recorded in the noise-exposed group of rats might indicate an effect of stress [as observed with thymus rebound and thymic hypertrophy or atrophy in adult humans (Nishino et al. 2006)] and/or an immune effect. Thymus hyperplasia has already been correlated with chronic exposure to noise in female adult rats (Zymantiene et al. 2017). Unfortunately, we only measured the weight of the thymus at 9 wk of age, when the organs involved in the immune system had still not matured.

Conclusion

In accordance with our starting hypothesis, subchronic high-level noise exposure was associated with sleep perturbations, hyperphagia, and weight gain. The recorded sleep modifications were more marked during noise-free periods (a greater amount of REM sleep during the active period and especially during the 1-h daytime plethysmography recording, and a greater TST and a lower NREM/REM sleep ratio during the active period) than during the rest period of exposure, suggesting the presence of after-effects. The noise-exposed animals ate and drank more and also displayed higher mRNA expression levels of leptin receptors and *CART*. These homeostasis-related parameters and the expression of leptin receptors and *CART* are known to be stress markers and so might indicate a greater risk of metabolic and immune disorders in the noise-exposed juvenile rats studied here.

Table 6. mRNA Expression in noise-exposed group ($n = 12$), expressed as $2^{-}\delta\delta Ct$ [fold induction over the expression level in the control group ($n = 11$), set to a value of 1].

Gene	Control group	Noise-exposed group	Group comparison
Leptin receptor	1	0.629 ± 0.160	$p = 0.030$
CART	1	1.331 ± 0.140	$p = 0.037$
POMC	1	1.426 ± 0.310	NS
NPY	1	1.2770 ± 0.220	NS

Note: Values expressed in mean ± standard error of the mean. Noise-exposed group was exposed to noise at an intensity of 87.5 decibels (dB) and frequencies between 50–20,000 Hz for 5 wk and 2 d during the 12-h rest period. *CART*, cocaine- and amphetamine-regulated transcript; NS, nonsignificant; *NPY*, neuropeptide Y; *POMC*, pro-opiomelanocortin. *p*-Values represent significant differences compared with control group. All gene expression was normalized to *GADPH* gene expression only in final calculation.

Acknowledgments

We thank Professor J. Libert for helpful discussions, and D. Fraser, Ph.D. (Biotech Communication SARL, Ploudalmézeau, France), for reviewing and revising the manuscript's English. We also thank L. Didier at the PlatAnn facility for his help.

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